RECOGNIN VACCINES

Cross references to Other Applications

This application is a Continuation-in-Part of my application Serial No. 07/744,649 filed 08/08/91, and the prior applications of which it is in turn a continuation-in-part, Serial Nos. 941,940,852,200, 621,112, 553,075, 550,432, 450,404, 385,451, and 922,799, which should be incorporated by reference in the present application.

THE INVENTION

This invention is directed to the discovery of products and methods to aid in the prevention of cancer, or its treatment, through the administration of a vaccine, or of the products produced by the vaccine, to destroy or inhibit the growth of cancer cells regardless of cell type.

The present invention teaches two ways of strengthening immune defenses against cancer: the administration of either 1) a specific antibody (anti-Recognin) itself, or 2) a derivative of a Recognin, to produce both the antibody and the cellular part of the immune response - thus a vaccine for cancer.

In 1959, Dr. Lewis Thomas, and later Dr. MacFarlane Burnet theorized that there might be an ongoing immune process throughout normal life - immunosurveillance - to detect and destroy any cancer cells which might arise. However, there was no evidence to support this theory. In recent years, indirect evidence has suggested that immune processes somehow protect people from acquiring cancer. But until now there has been no direct evidence of these processes in humans. Thus for example some such process might be assumed to exist because in immunodeficient disorders as AIDS, the incidence of cancer is markedly increased. However, in these immunodeficient disorders where there are causative agents such as the HIV virus, the increased incidence of cancer might be due to a carcinogenic effect of the virus itself on cells which, since the Rous sarcoma virus, has been known to exist for several viruses. Therefore, because of the lack of any direct evidence of immunosurveillance

in humans,the idea has been largely abandoned.

It was therefore totally unexpected to find in the present invention that the anti-Recognin antibody increases in concentration with age in healthy non-tumor bearing individuals between the third and the seventh decades as the risk of cancer increases. The anti-Recognin increases even more when clinical cancer appears. In the present discovery, the antibody also was shown to return to normal when the cancer is successfully treated.

In the present invention, the anti-Recognin also was shown to kill or inhibit the growth of cancer cells.

In addition, Anti-Recognin was found bound to cancer cells removed at surgery or at autopsy.

While anti-Recognin was shown to be elevated during the presence of clinical cancer, there was no evidence to suggest that anti-Recognin functions to protect humans against cancer before it becomes clinically evident. Therefore there was no reason to assume that the development of a vaccine composed of a Recognin or its derivatives would protect against the development of clinical cancer, or help to destroy it once it had begun. The present invention describes products to aid both cancer prevention and cancer treatment.

Cancer treatment is most successful when the cancer is detected early. Anti-Recognin antibody increases in concentration with a wide variety of cancer cell types, rather than just a particular cell type, and is quantitatively related to survival in patients.

Cancer development involves the "transformation" of the cells to the malignant state and the "proliferation", or the

multiplication of the transformed cells. The malignant cells multiply out of control until they become a palpable mass, or erode a blood vessel causing bleeding. The mass or bleeding may be the first clinical symptoms of cancer. Until now, there has been no way to know when transformation has occurred except by performing microscopic examination of tissue taken during surgical biopsy. In seeking to detect and treat breast cancer, for example, women are advised to examine their breasts regularly for lumps. According to the American Cancer Society (ACS), by the time a lump can be felt, the cancer has progressed further than is ideal for treatment; Therefore the ACS advise regular mammograms. But from a recent conference at the National Cancer Institute in Bethesda, it appears that mammograms do not help the survival rate at all for women below the age of 50, and only improve survival approximately 30% after 50 years of age.

Mammography and other cancer detection techniques can now be assisted by the blood test for the concentration of anti-Recognin antibody. An increase in this antibody occurs in over 90% of patients with early breast cancer. The antibody may be elevated when the breast cancer is so small that it is missed on biopsy examination. Two such missed tumors were detected on reexamination of biopsy specimens. In another group of 170 normal individuals, only five had elevated anti-Recognin tests. Four of these five (three in their 30s) developed cancer in sites other than the breast within three years.

Cells which have undergone malignant transformation in humans may take years to, or may never, proliferate to become clinical cancer[1]. If inhibition of proliferation is an immune

process, as has been theorized[2,3] there is no direct evidence in human cancer of such an immune process, and the responsible mechanisms are unknown. Anti-Recognin, specific for highly antigenic 10K cancer cell membrane oncoproteins[4-6], is a human IgM antibody which increases in concentration in clinical cancer regardless of cell type, and is quantitatively related to survival in patients[7-13]. *In vitro*, antigen-purified human anti-Recognin is here shown to be present in non-saturating amounts on cancer cells removed at surgery or autopsy, to be cytotoxic to malignant glial cells, and inhibitory to the growth of small cell lung carcinoma cells at picograms of antibody per cell. *In vivo*, anti-Recognin concentration is shown in healthy humans without tumors to increase each decade between the fourth and the seventh; to increase markedly at the diagnosis of breast cancer; then to have returned to the normal range 0.1 to 27 years after successful treatment. Taken together, these properties suggest that anti-Recognin is a general inhibitory transformation antibody whose augmentation may be useful in efforts at the immune prevention and treatment of cancer.

In glioblastoma, the normal 250,000 Dalton membrane glycoprotein 10B which has been associated with recognition phenomena in the brain[14] is replaced by the Recognin precursor glycoprotein, which has 50% less carbohydrate and is overproduced 7 to 10 fold relative to the concentration of 10B in normal brain[4-7]. When malignin was produced as the immunogenic fragment of the precursor it was thought to be a cell-type-specific cancer marker[4]. It was only when similar 10K peptides with identical

immunoreactivity were produced from MCF7 breast cancer cells (Recognin M) and from P3J lymphoma (Recognin L)[5] that malignin appeared to be a more general cancer antigen. An antibody to Recognin was shown to be elevated in patients with brain malignancies, both primary and secondary[4], and then surprisingly, elevated in all other malignancies tested[10-13]. The notion of a general cancer antigen and antibody was difficult to accept. However, this conclusion was supported by the demonstration that anti-Recognin was increased in concentration in patients with a wide variety of cell types of cancer in 3,315 serum specimens from cancer patients and controls determined blind by three independent laboratories[10-13]. Anti-Recognin has been isolated from human serum[6], produced in mouse monoclonal form[9], and produced *in vitro* by human lymphocytes challenged by the antigen Recognin[8]; and in all these cases has been shown to be an IgM[8].

REFERENCES CITED IN TEXT, EXAMPLES, AND LEGENDS FOR FIGURES

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EXAMPLE 1

To test further whether anti-Recognin is indeed an antibody specific to the process of malignancy rather than to a particular cell type, and to malignancy only, Recognin was demonstrated immunocytochemically in several cell types of malignancy. Figure 1, a through 1,g, shows the Recognin to be localized in cytoplasmic and outer cell membranes. Figures 1h and 1i show the specificity of anti-Recognin in binding selectively to two blast cells, but not to normal red and white blood cells in the same smear.

LEGEND FOR FIGURE 1: Immunostaining of malignant cells with antimalignin antibody. a. squamous cell carcinoma of lung, cells obtained by bronchial washing; b. scirrous carcinoma ofbreast, fresh frozen section; c. retrobulbar malignant neuroectodermal tumor, fresh frozen section; d. carcinoma of pancreas, MIAPACA cell culture; e. lymphoma, single cell from pleural fluid; f. carcinoma of the vulva cells, frozen smear; g. small cell carcinoma of lung, alkaline phosphatase stain; h. acute lymphatic leukemia, two blast cells in blood smear, both fluorescent and natural light are on together; i. same slide as in h., but with natural light turned off and only fluorescent light on; j., k., and l. cytotoxicity of 50 microlitres of anti-Recognin antibody, 10 micrograms/ml, left in contact for varying periods of time with glioblastoma brain cancer cells growing on wall of tissue culture flask: j. 30 minutes at 5o C; k. 45 minutes at room temperature; l. one hour at room temperature, before the second layer for visualization was applied. METHODS. Tissue specimens removed at surgery or autopsy were embedded in OCT gel on cryomold specimen molds and cryostat sections approximately 7-8 microns thick were placed on standard glass slides and kept at -20° C for at least 24 hours before use. Alternatively, tissue was deposited on the slide by "touch prep" technique and either immediately stained or fixed with 100% acetone or 95% ethanol at 4° C before staining. 50 microlitres of antimalignin antibody, 10 microgram per ml, purified by adsorption to immobilized malignin as in the method for its quantitative determination in the legend for Table 1, or of PBS for controls,

was applied to the section for 30 minutes at 4°C, rinsed in 0.5 M Tris buffer for five minutes at room temperature. For visualization, either a) a second layer of fluorescein labelled goat anti-human immunoglobulin was applied for one hour, rinsed in 0.5 M Tris buffer for five minutes at room temperature, and the slide viewed with light and fluorescent microscopy; or b) an alkaline phosphatase method of visualization was used.

EXAMPLE 2

While anti-Recognin given intravenously has been shown to bind preferentially to malignant glioma cells in the rat brain *in vivo* [7] it was not known whether the antibody actually binds to cancer cells in humans *in vivo*. Human cancer tissue freshly excised at surgery and at autopsy was therefore examined for the presence of anti-Recognin antibody[15]. Table 1 shows that anti-Recognin can be eluted from these tissues. All of the exposed Recognin sites are not covered by antibody since before antibody elution cancer cells can be immunostained with anti-Recognin (Fig. 1).

TABLE, EXAMPLE 2 Elution of Anti-Recognin Antibody Bound to Human Cancer Cells *In Vivo*

			ug /ml medium or buffer /mg tissue, mean+/-S.D.	
Eluant	Tissue	N	Slow-Binding Antibody (2 Hours)	Fast-Binding Antibody (10 Minutes)
L15 medium	Cancer	6	0.97 +/- 0.65	0.47 +/- 0.5
	Normal	4	0.10 +/- 0.14	0.14 +/- 0.12
Glycine buffer, pH 2.4	Cancer	3	0.27 +/- 0.12	0.36 +/- 0.17
	Normal	2	0.02 +/- 0.02	0.03 +/- 0.04

LEGEND FOR TABLE in EXAMPLE 2: METHODS. Normal tissue (muscle, liver and brain), and cancer tissue (adenocarcinoma, transitional cell carcinoma, neuroblastoma, and lymph node metastases) removed at surgery and autopsy was placed in sterile Leibovitz Medium L15 plus antibiotics (Penicillin-Streptomycin-Fungizone Mixture, 1ml/100 ml. of medium) (Grand Island Biological Co., Grand Island, N.Y.). Approximately 5 mm cubed pieces of tissue were trimmed of extraneous material, weighed in sterile plastic Petri dishes, and minced into less than 1 cu mm pieces with sterile blades, then suspended in either 5 ml of L15 medium for 2 hours, or in 5 ml of glycine buffer pH 2.4 for 15 minutes, cultured at 37°C in a humid

container. N refers to the number of separate tissue specimens studied with each eluant. Each eluant was coded for blind determination, shipped overnight in dry ice to the laboratory, and the next day, quantitatively determined for antimalignin antibody determined with immobilized malignin antigen (TARGET reagent, Brain Research, Inc., Boston). In the preparation of TARGET reagent, as previously described[15], human glioblastoma cells were grown in 250 ml sterile tissue culture flasks stacked in the horizontal position in a 37°C incubator until a monolayer of cells had covered the wall of the flask, freed from the wall with trypsin, scraped with spatula into a glass beaker, homogenized with a Branson sonifier, dialyzed, concentrated by perevaporation, centrifuged, chromatographed on a Cellex D column with stepwise elution with bufered solutions of decreasing pH, with the protein in each eluate quantified by adsorption at 280 mu. The last eluate, which contains malignin,eluted at its pK of approximately 2.7, was rechromatographed. The final preparation contained malignin with the following composition: Glu13Asp9Thr5Ser5Pro4Gly6Ala7Val6Met2Ileu4Leu8Tyr3 Phe3His2Lys6Arg51/2Cys1, and demonstrating a molecular weight of approximately 10K, and dimers and trimers thereof, on SDS gel and thin layer gel chromatography. Malignin was combined covalently with bromoacetylcellulose to produce immobilized TARGET reagent . To quantify the antimalignin antibody in cancer and normal tissue eluants, 0.2 ml samples of each eluant, in duplicate, were exposed to TARGET reagent with shaking for either two hours or 10 minutes, the bound antibody washed three times with cold NaCl, then released from the antigen by incubation with shaking with

0.25 molar acetic acid, centrifuged at 3000 rpm, the clear acetic acid supernatant read spectrophotometrically at O.D. 280, and the results converted to micrograms of protein. Results are given, as mean +/- S.D. for each group of tissues and each eluant, for slow-binding antibody (2 hour contact of eluant with immobilized malignin) and fast-binding antibody (10 minute contact of eluant with immobilized malignin), microgram/ ml eluant / mg. original tissue[16].

EXAMPLE 3

That anti-Recognin is an IgM has been confirmed by the quantitation of human serum anti-Recognin in a luminescent plate assay by reacting the bound anti-Recognin with goat anti-human IgM specific for mu chains.

EXAMPLE 4

To determine whether other IgMs would bind to Recognin, 7 mg. of non-specific serum IgM (Sigma) was added to 20 micrograms of immobilized Recognin malignin as in the method described in the legend for Table in EXAMPLE 2; only 200 nanograms of this non-specific serum IgM was bound, in contrast to >500 micrograms of anti-Recognin IgM (Figure 3).

EXAMPLE 5

The effect of anti-Recognin on cancer cells *in vitro* is demonstrated by its cytotoxicity (Figure 1j through 1l).

EXAMPLE 6

The effect of anti-Recognin on cancer cells *in vitro* is demonstrated by its growth inhibition properties (Figure 2) which occur in the range of picograms/cell.

LEGEND FOR FIGURE 2 in EXAMPLE 6: Inhibition of growth of

small cell lung carcinoma cells in vitro by anti-Recognin antibody. The inhibition is proportional to the concentration of anti-Recognin, which was 50% effective in the picogram per cell range. Each bar in the Figure represents the mean +/-SD for 24 wells, that is, from 3 wells for each of eight separate preparations of anti-Recognin at each dilution. METHODS. Small Cell Lung carcinoma cell line UCHNCU, grown in suspension and maintained in RPMI 1640 10% FCS (fetal calf serum) was seeded in 96 well microtitre plates (round bottom) at 104 cells per well. Serial dilutions were made of anti-Recognin antibody which had been purified by adsorption to immobilized malignin so that final concentration of anti-Recognin in RPMI FCS was 1/6 to 1/1458; final total volume per well was 200 microlitres. Plates were incubated at 37^{o}C in 6% CO2 /air for 3 days. On day 3 cultures were pulsed with 1 uci/well tritiated thymidine (3HTdR) for 6 hours, then cultures were harvested with automatic cell harvester on filter pads. Filters were dried for 2 hours in 37oC dry incubator, discs were placed into scintillation vials, 2 ml Optiphase scintillant added, tubes capped , cpms counted on Beckman LS 1800 beta counter and % Inhibition calculated as Control-Experimental/ Control x 100.

EXAMPLE 7

That humans who do not have benign or malignant tumors have appreciable anti-Recognin antibody in their serum[4,10-13] requires explanation.We have now discovered that the concentration of this antibody in non-tumor bearing humans increases with age (Figure 3).

LEGEND FOR FIGURE 3 in EXAMPLE 7. Increase in concentration of serum anti-Recognin (antimalignin) antibody with age in individuals without tumors, and in human clinical breast cancer; and its return to normal after successful treatment. Each data point represents the mean (+/- standard deviation) concentration of antimalignin antibody. "N" indicates the number of specimens per data point. "Age in years, Normal Non-Tumor ": specimens from normal individuals without benign or malignant tumors: from the left, the first five points are one for each decade of age from the 3rd through the 7th; the sixth point is for ages 71-90. The 7th through 10th points represent 4 clinical states. 7th point: "Benign Breast Dx (Diagnosis)" - patients with a variety of mammographic anomalies judged benign on cytopathological examination; 34/35 were in the normal range of antibody concentration(<135 ug/ml) (see text for discussion of 'false positive' results). 8th point: "Breast Cancer at Dx (Diagnosis)": patients at time of diagnosis of breast cancer; these were all in the elevated range (135 or > ug/ml). 9th and 10th points: "Post Rx" data are 0.1 to 1 year, and 2 to 27 years respectively after successful treatment of breast cancer. The ages in years (mean+/-SD) of the patients for the 7th through 10th points were respectively 47.3(+/-11), 56.2(+/-12), 51.0(+/-11), and 53.2(+/-13). METHODS: 2,194 specimens were received at random from 25 centres in the US and 2 in the UK. Determinations were performed blind in three independent laboratories. All specimens were collected in unsiliconized BD #6440 vacutainer tubes (Becton Dickensen Co.), the sera shipped in dry ice and determined blind within 24 hours by reacting 0.2 ml of serum with immobilized

malignin in duplicate as previously described[16](see legend for Table in EXAMPLE 2).

An increase with age of a cancer-related immune mechanism, in this case an antibody inhibitory to cancer cells, in the non-cancer normal population to our knowledge has not previously been described. That this increase is temporally correlated stepwise with the increased risk for developing cancer with increasing age suggests that its function is what it appears to be: that is, part of an immunosurveillance process for which hitherto there has been no direct evidence in humans. Either genetically programmed and anticipatory, or simply as a continuing response to the appearance of the transformation antigen Recognin, the anti-Recognin antibody response could accompany the intermittant or continuous appearance of transformed cells, with the resultant suppression of these cells (see Figure 2). This normal inhibitory activity might be increased in benign tumors, a state of cell hyperplasia in which the frequency of transformation would be expected to be greater than normal (see data below, and Figure 3). The proliferation of transformed cells would result in the marked elevation in anti-Recognin concentration above normal levels, and clinical evidence of cancer. This is seen to occur in breast cancer at the time of diagnosis (Figure 3). Figure 3 also shows that marked elevation of anti-Recognin is not stigmatic, but disappears after successful treatment; in 83% of patients from 0.1 to 1 year after treatment, and in 96% of patients from 2 to 27 years after treatment resulting in 'no clinical evidence of cancer', whether achieved by surgery or other therapy.

One limitation of studies which correlate anti-Recognin

levels before biopsy with cytopathological findings at biopsy is that anti-Recognin may be elevated when the malignancy is small enough to be missed on cytological examination, as when the tumor is only 1 mm in diameter[10] or smaller, as 1) in the present study where only a few malignant ducts were seen in one corner of one section, 2) in two such breast tumors out of seven proven to be malignant only on repeated examination and 3) possibly but not proven in 12 of 22 cases of breast tumor judged benign on cytology. That such supposed 'false positive' anti-Recognin elevations may represent early warning of malignancy is illustrated by a group of 170 healthy individuals first studied in 1988-89 of whom only five had elevated antibody (2.3%): four of these five (of whom three were in their 30s) developed clinical cancer within three years.

These results clearly indicate a process for quantitatively assessing the immune status of an individual human or animal with regard to the level of their anti-cancer defences, and with regard to whether malignant cells are present or not, by determining the quantity of anti-Recognin antibody and the quantity of immune cells specific for malignin and Recognins L and M in their serum or other body fluids or tissues.

Since anti-Recognin increases in concentration with age in non-tumor bearing humans, is markedly elevated when transformed cells are clearly present, and this elevation disappears when there is no longer evidence of the presence of transformed cells, we have called anti-Recognin a transformation antibody; to our knowledge the first so described. The antigen is not restricted to one cell type; the antibody is general. The earlier finding by

actuarial survival studies that the duration of survival in cancer patients is quantitatively related to the concentration of anti-Recognin[12,13], taken with the present demonstration that anti-Recognin is cytotoxic and inhibitory to cancer cells, and that some but not all sites on cancer cells *in vivo* are covered by anti-Recognin, together indicate that an effort to augment this inhibitory antibody by administering the human antibody itself, or a derivative of a Recognin (a derivative of malignin, Recognin L or Recognin M) as vaccine to stimulate both the cellular and humoral elements, can be useful in efforts at the immune prevention and therapy of cancer.

EXAMPLE 8

The Recognin derivative vaccine can be any product larger, smaller or the same molecular weight which contains the immunological specificity of malignin, Recognin L or Recognin M, (see U.S. Patent No. 4,976,957 (S.N.07/744,649) and the applications of which it is a continuation-in-part as listed above incorporated herein by reference) can be used. The vaccine can be entirely produced from tissues or cells, or it may be entirely synthetic, or any combination of the two. For example the Recognin derivative vaccine malignin glycoprotein precursor, molecular weight approximately 250,000 Daltons, or any fraction thereof which contains the immunological specificity of malignin, Recognin L or recognin M can be administered as vaccine to individual humans or animals for example, but not exclusively, in doses of approximately 1 mg or more subcutaneously, and the quantity of anti-Recognin determined by the methods shown in Example 2 as well as changes in immune cells, such as B cells, T-cells, both helper

and suppressor, macrophages, before and after the administration of vaccine. The level of anti-Recognin will increase approximately 10 days after the first administration of vaccine. Regardless of whether the increase has occurred, a second dose of vaccine is given after the blood specimen is taken for anti-Recognin determination, and 10 days later, a third blood specimen is taken for anti-Recognin determination and a third dose of vaccine is administered. Thirty days after the first dose of vaccine is administered, the anti-Recognin level should be at a maximum. Additional booster doses of vaccine may be given to maintain the level of antibody achieved and depending upon the degree of risk of cancer exhibited by the subject. For example in a family in which the grandmother, mother, and each of the two sisters have developed breast cancer, for the remaining sister who is receiving the vaccine the physician in charge may decide that more frequent boosters are required. Where the vaccine is used for prevention, the changes in anti-Recognin and immune cells will be followed. Where the vaccine is used in treatment of already present clinical cancer, all clinical and laboratory determinations appropriate to the type of cancer and its stage (eg. CATSCANs, MRI, blood counts in hematological malignancies, etc.) also will be followed for evidence of beneficial effect.

EXAMPLE 9

The administration of a product such as DNA or RNA to humans or animals which is specific for the production of a Recognin or a derivative thereof, which contains the immunological specificity of malignin, Recognin L or Recognin M, if such DNA or RNA is administered so as to be incorporated by the genome or the

protein synthesizing apparatus respectively, this will in turn cause to be inhibited or destroyed cancer cells, regardless of cell type, and prevent the development of clinical cancer, or if it has already developed, treat clinical cancer.

EXAMPLE 10

The administration of a product which has the characteristics of an antibody to malignin and the Recognins L and M will cause to be inhibited or destroyed cancer cells, regardless of cell type, and prevent the development of clinical cancer, or if it has already developed, treat clinical cancer. This product can be the whole antibody of a fragment thereof, the antibody alone, or bound to an additional agent which is cytotoxic to cancer cells.

EXAMPLE 11

A product which has the characteristics of a cell or mechanism with immunological specificity for malignin and the Recognins L and M, where the cell is any cell which will destroy or inhibit the growth of cancer cells such as a T cell, a B cell, a phagocytic cell, or a device or mechanism which when in contact with cancer cells would bind, adsorb or engulf them so as to destroy them and /or remove them from the body such as a filter or column or resin or surface through which or on which the cancer cells are made to pass or come in contact, is useful to treat clinical cancer.